Smokeless Tobacco and Disease: Evidence Related to Long-term Safety of Nicotine

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Nicotine in ST Products

Product	Nicotine (mg\gm tobacco; range)
Chewing Tobacco	9.9 (3.4 – 39.7)
Dry Snuff	16.8 (10.5 – 24.8)
Moist Snuff	12.6 (4.7 – 24.3)
Cigarette Tobacco	- (9.5 – 13.4)

Health Concerns with ST

- Oral Disease
- Cancer
- Cardiovascular Disease
- Reproductive Disorders

NICOTINE AND CANCER: Mechanistic Concerns

- Nicotine metabolism to a carcinogenic nitrosamine
- Nicotine inhibition of apoptosis – possible impairment in killing cancer cells
- Nicotine promotion of angiogenesis
  – possible promotion of tumor growth

ST and Cancer: Epidemiology

- Oral cavity
- Pancreatic
- ? Gastroesophageal

Use of Swedish Snus Associated with Increased Risk of Pancreatic Cancer

(Luo et al, Lancet 2007)

279,897 Male Swedish Construction Workers 1978-1992

	OR*	95 % CI
Snus Users	2.0	1.2 – 3.3
Smokers	2.8	2.1 – 3.7

The lack of increase in common cancers in lifelong ST users indicates that nicotine is not a general cancer promoter

ST and Cardiovascular Disease

	Strength of Evidence
Hypertension	±
Myocardial Infarction	+
Stroke	+
Diabetes and Metabolic Syndrome	+
Dyslipidemia	+
Other CVD Biomarkers (CRP, TxA2, fibrinogen)	-

ST and Myocardial Infarction

Meta-analysis	N	RR	95% CI
Lee, 2007	8	1.12	0.99 – 1.27
Boffetta, 2009	11	1.13	1.06 – 1.21
Sweden only	5	1.06	0.83 – 1.37

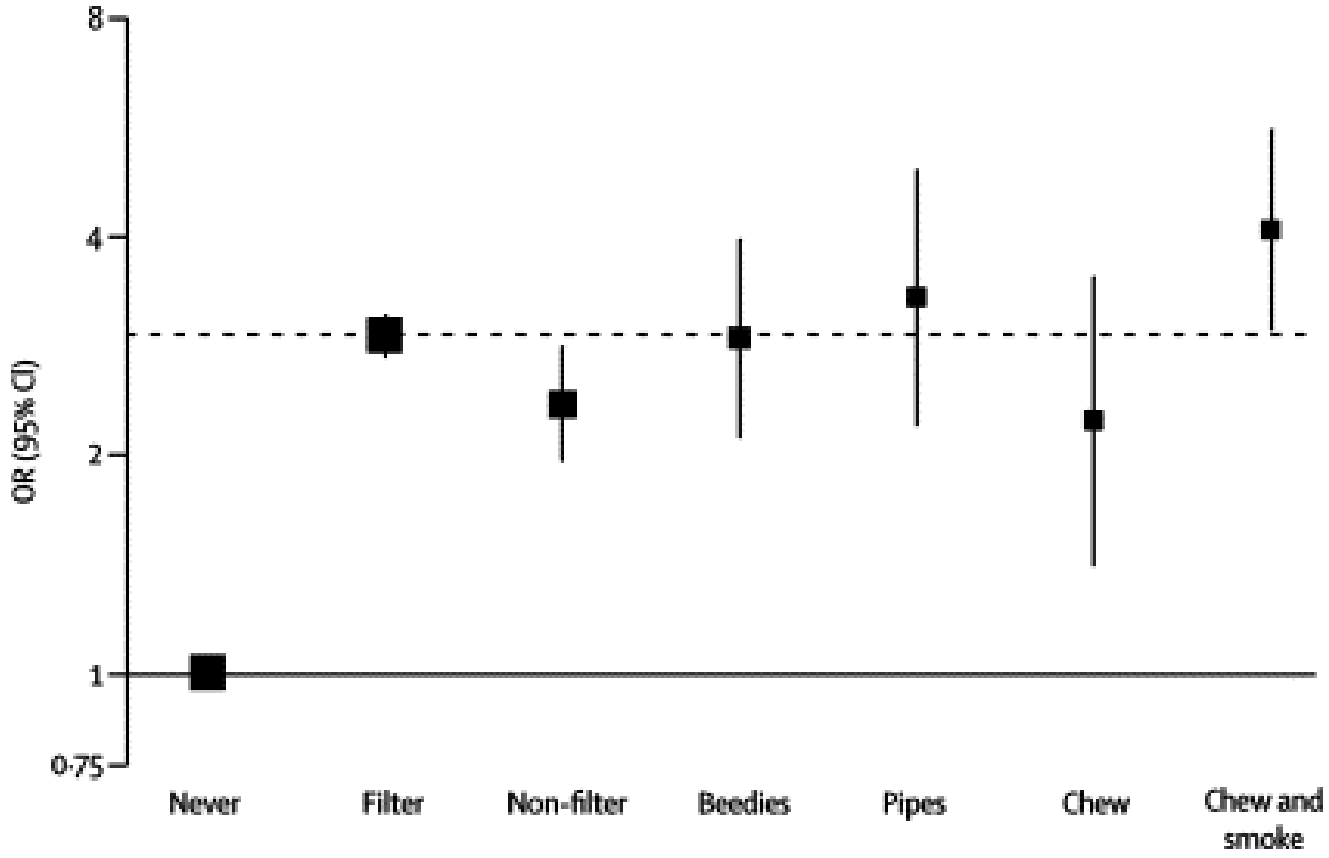
Tobacco Use and Risks of Myocardial Infarction
INTERHEART Study
(Teo et al, Lancet 2006)

52 countries

12,411 cases nonfatal MI

14,637 controls

Risks of Acute MI and Type of Tobacco Used



ST and Stroke

Meta-analysis	N	RR	95% CI
Lee, 2007	5	1.42	1.29 – 1.57
Boffetta, 2009	5	1.40	1.28 – 1.54

Meta-analyses showing increased risk of MI and stroke in ST users are heavily weighted by CPS-I and CPS-II, which are older US studies with many methodologic problems. More recent Swedish studies and an NHANES study indicate minimal if any increased risk of CVD with ST.

Adverse Pregnancy Outcomes in Snuff Users

(England et al Am J Obstet Gynecol 2003; 189:939)

Population-based cohort study in Sweden
Women with singleton, live-born infants
789 snuff users; 11,240 smokers; 11,995 non-users

	Reduction in Birth Weight (gm)	Preterm Delivery (OR)	Preeclampsia (OR)
Snuff Users	36 (6-72)	1.98 (1.46-2.68)	1.58 (1.09-2.27)
Smokers	190 (178-203)	1.57 (1.38-1.80)	0.63 (0.53-0.75)
1-9 CPD	172 (158-185)	1.50 (1.30-1.74)	0.71 (0.59-0.88)
$\geq$ 10 CPD	224 (207-240)	1.71 (1.44-2.04)	0.48 (0.36-0.69)

Extrapolating ST Studies to Questions of Nicotine Safety

- No evidence that nicotine causes or promotes cancer
- Nicotine may slightly increase the risk of MI and stroke. If so the risks are far lower than those of cigarette smoking
- Nicotine likely has adverse effects on reproduction, including increasing the risk of pre-eclampsia and preterm birth